Complete Summary

GUIDELINE TITLE

Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Morgan SC, Waldron T, Eapen L, Mayhew LA, Winquist E, Lukka H, Genitourinary Cancer Disease Site Group. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Feb 21. 28 p. (Evidence-based series; no. 3-17). [45 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Pathologic T3 or margin-positive prostate cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate if adjuvant radiotherapy following radical prostatectomy improves clinically important outcomes in patients with pathologic T3 or margin-positive prostate cancer

TARGET POPULATION

Men who have undergone radical prostatectomy for clinically localized prostate cancer and who have been found to have either tumour extension beyond the prostatic capsule (pT3a), seminal vesicle invasion (pT3b), positive resection margins (R1), or more than one of these features

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant external beam radiotherapy versus observation

MAJOR OUTCOMES CONSIDERED

The primary outcome of interest is overall survival.

Outcomes of secondary interest include:

- Prostate cancer- specific survival
- Metastasis-free survival, biochemical progression-free survival, locoregional recurrence-free survival, time to initiation of androgen deprivation therapy, incidence of acute and late toxicity, and quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Relevant articles were identified by searches of MEDLINE (1966 – February 2008 week 2), EMBASE (1980 – 2008 week 7), and The Cochrane Library (2007, Issue 4). In MEDLINE, "prostatic neoplasms" (Medical Subject Heading [MeSH]) was combined with "prostatectomy" (MeSH) and "exp radiotherapy" (MeSH). Variations of the following phrases were used as text words: "prostate cancer," "prostate carcinoma," "prostate adenocarcinoma," "prostatectomy," "adjuvant radiation," "postoperative radiation," and "postprostatectomy radiation." These terms were then combined with search terms for the following study designs or publication types: randomized controlled trials, controlled clinical trials, meta-analyses, systematic reviews, and practice guidelines. The EMBASE search was adapted using Excerpta Medica tree terms. The complete MEDLINE and EMBASE search strategies are detailed in Appendix 1 in the original guideline document.

The conference proceedings of the annual meetings of the American Society of Clinical Oncology (2000-2007), the American Society for Therapeutic Radiology and Oncology (2000-2007), and the American Urological Association (2002-2007) were also searched for relevant trials. Where relevant abstracts were identified, supplementary online resources (i.e., slides from accompanying presentations) were also searched for additional data.

The reference lists of eligible trials were searched for relevant articles. Expert colleagues and collaborators were also asked to identify any relevant unpublished or published trials not otherwise identified.

Study Selection Criteria

Articles were eligible for inclusion in the systematic review if they met the following criteria:

- They were randomized controlled trials (RCTs) (published or unpublished, full articles, or abstracts) that compared adjuvant radiotherapy (RT) in the immediate postoperative period after prostatectomy to observation with therapies (i.e., RT, androgen deprivation therapy [ADT], or any other therapy) held in reserve for salvage, in patients with prostate cancer with either tumour extension beyond the prostatic capsule (pT3a), seminal vesical invasion (pT3b), positive resection margins (R1), or more than one of these features. No limitations were placed on neoadjuvant ADT. However, trials in which the adjuvant RT arm included adjuvant treatment modalities in addition to RT (e.g., concurrent ADT) were ineligible.
- They were systematic reviews or evidence-based clinical practice guidelines that addressed the research question.
- They were published in English.

NUMBER OF SOURCE DOCUMENTS

A total of 14 reports representing three randomized trials satisfied the eligibility criteria. A single systematic review without meta-analysis was also identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

All studies identified by the literature search were assessed against the above selection criteria independently by two reviewers. Discrepancies regarding eligibility were resolved by consensus. Methodologic quality of the eligible studies was assessed by the same two reviewers with respect to the following parameters: whether treatment allocation was genuinely random and concealed from the trialists, whether there was a description of patient withdrawals and dropouts, and whether analyses were performed by intention-to-treat. The criteria were rated as "met," "unmet," or "unclear". Data extraction was performed by a single reviewer using pre-designed forms while a second reviewer acted as an independent auditor to verify accuracy of the data extraction.

Overall survival, prostate cancer-specific survival, metastasis-free survival, biochemical progression-free survival, locoregional recurrence-free survival, time to initiation of androgen deprivation therapy (ADT), acute and late toxicity, and quality of life were the outcomes of interest. When data were available on these outcomes from two or more trials, meta-analysis of the trial data was planned using the Review Manager software (RevMan 4.2.8) provided by the Cochrane Collaboration (Metaview © Update Software). The hazard ratio (HR) is the preferred statistic for pooling time-to-event outcomes because it incorporates data from the entire Kaplan-Meier curve and allows for censoring. When available, the HR was extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CIs) or p-values using the methods described by Parmar et al. These values were entered directly into RevMan 4.2.8 using the "generic inverse variance" method. A random effects model was used for all pooling as it provides a more conservative effect estimate. Pooled results are expressed as HRs with 95% CI. HRs less than one favour adjuvant radiotherapy (RT), whereas HRs greater than one favour observation.

The meta-analysis results were assessed for heterogeneity by visual inspection of the forest plot and by calculating the Chi-square test for heterogeneity and the I^2 percentage. A probability level for the Chi-square statistic of less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity, and I^2 values of 25%, 50%, and 75% were indicative of low, moderate, and high degrees of heterogeneity, respectively. Sensitivity analyses were performed in the event of heterogeneity or to explore the effects of trial quality on the meta-analysis results.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Overall survival is certainly the outcome of greatest importance for any cancer therapy, incorporating the effect of mortality secondary to cancer, the interventions used, and all other causes. Given the relatively indolent natural history of prostate cancer, the expectation is that lengthy follow-up is necessary to assess differences in overall survival, and the results of this review bear this out. Neither the Southwest Oncology Group (SWOG) nor the European Organization for the Research and Treatment of Cancer (EORTC) trial detected a survival benefit with adjuvant RT; median follow-up times were 10.6 years and five years in each trial, respectively. A meta-analysis of the survival data from these two trials also did not demonstrate a statistically significant result. Follow-up at this time is simply not long enough to accurately determine if adjuvant radiotherapy (RT) is associated with a survival benefit. Updates of this review and meta-analysis are planned as the data mature and as new trial results become available. It should also be borne in mind that for neither trial was overall survival the primary endpoint; as such, neither trial was specifically powered to detect a difference in overall survival between the two arms. This is of particular relevance to the SWOG trial, in which only 431 patients were randomized.

Biochemical progression is a controversial surrogate marker for other prostate cancer outcomes. The meta-analysis performed of these data unequivocally demonstrates that, compared to observation, adjuvant RT confers a major reduction in the rate of biochemical failure. The magnitude of benefit in this endpoint is remarkably similar across the three included trials. As prostate-specific antigen (PSA) progression is often a trigger for initiation of androgen deprivation therapy (ADT), it is not surprising that a reduction in ADT use of similar magnitude was also observed.

While time-to-event analyses for freedom from locoregional recurrence are not available and the sole analysis for freedom from metastasis did not demonstrate a significant benefit from adjuvant RT, two of the trials report an outcome that is a composite of locoregional failure and metastasis - clinical progression-free survival. Both trials reported a significant improvement in this outcome with adjuvant RT. On the basis of these data, adjuvant RT does therefore significantly reduce locoregional and distant recurrences when considered together.

A major shortcoming of the trials included in this review relates to the management of patients in the observation arms of these trials. In short, none of the trials employed a definite protocol as to how and when PSA and clinical failures should be treated. As a consequence, there was considerable variability in patient management in these arms (see Table 1 in the original guideline document). It may be argued that, in many cases, local intervention with RT was delayed until such time as it was unlikely to be effective. The ongoing RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) trial addresses this shortcoming. Once completed, it is hoped that this trial will serve

to clarify the optimal timing of RT and the role for ADT following radical prostatectomy (RP) in patients with high-risk pathologic features.

Comparing toxicity data across the three trials is made difficult by differences in the reporting of toxicity data. In the SWOG trial, significantly greater rates of urethral stricture, urinary incontinence, and rectal complications were seen in irradiated patients compared to those randomized to observation. Caution must be used, however, in interpreting the toxicity data from the SWOG study. As noted above, toxicity was not recorded using a validated, graded toxicity-scoring instrument. Instead, complications were recorded only if annotated on study flow sheets. Such data are vulnerable to the bias that retrospectively collected unsolicited toxicities are more likely to be reported in the intervention arm. In the EORTC trial, where toxicity was graded prospectively using validated scales, it is clear that there is significantly greater minor ($\leq$ grade 2) acute toxicity in patients who receive adjuvant RT. However, there was no significant excess grade 3 or higher toxicity observed at five years of follow-up. As the late toxicity evaluations performed in the trials only considered genitourinary and gastrointestinal symptoms, the potential benefits of adjuvant RT in terms of sparing the systemic toxicity of ADT could not be assessed.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this evidence-based series (EBS) report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Genitourinary Disease Site Group (GU DSG) circulated Sections 1 and 2 to external review participants in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 104 external review participants in Ontario (73 urologists and 31 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on June 19, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GU DSG and the Report Approval Panel of the PEBC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

To date, adjuvant radiotherapy has not been shown to improve overall survival compared with observation. Longer follow-up from the completed randomized trials is required in order to accurately assess this outcome. On the basis of the available evidence, the Genitourinary Cancer Disease Site Group offers the following recommendations:

- Adjuvant external beam radiotherapy should be offered to patients with the goal of reducing biochemical failure, locoregional failure, and delaying or reducing the need for androgen deprivation therapy.
- Early referral following radical prostatectomy to a radiation oncologist for a discussion around radiotherapy is advisable.
- The decision regarding the use of adjuvant radiotherapy should take into account its modest associated genitourinary and rectal toxicity.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials and a systematic review without meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Two trials reported data on overall survival but neither demonstrated a significant difference in this outcome between adjuvant radiotherapy and observation arms. A meta-analysis of the data from the two trials also failed

to show a statistically significant improvement with adjuvant radiotherapy (hazard ratio=0.91; 95% confidence interval 0.67–1.22; p=0.52).
- All three trials reported data on biochemical progression-free survival and detected statistically significant reductions in biochemical failure with adjuvant radiotherapy compared to observation. A meta-analysis of these data produced a pooled hazard ratio of 0.47 (95% confidence interval 0.40–0.56; p<0.00001).
- None of the trials provided a time-to-event analysis for locoregional recurrence-free survival. At five years of follow-up, one trial reported that 15.4% (98% confidence interval 11.2–19.6) of those randomized to observation had experienced locoregional failure compared to 5.4% (98% confidence interval 2.7–8.0) of those randomized to adjuvant radiotherapy (p<0.0001).
- The benefit seen in metastasis-free survival with adjuvant radiotherapy did not quite reach statistical significance (hazard ratio=0.75; 95% confidence interval 0.55–1.02; p=0.06) in the one trial reporting this outcome.

POTENTIAL HARMS

All three trials reported on toxicity. In the trial that provided comparative graded toxicity data, there were no significant differences between arms in major gastrointestinal or genitourinary toxicity at five years.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The available data from randomized trials does not address:

- Adjuvant radiotherapy following radical prostatectomy versus early salvage radiotherapy.
- Adjuvant radiotherapy combined with androgen deprivation therapy.
- Optimal radiation dose fractionation and volume or radiotherapy technique.
- Nodal radiotherapy.
- Whether the magnitude of benefit from adjuvant radiotherapy varies across the various strata of high-risk disease (margin positivity, extracapsular extension, and seminal vesicle invasion).

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Morgan SC, Waldron T, Eapen L, Mayhew LA, Winquist E, Lukka H, Genitourinary Cancer Disease Site Group. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Feb 21. 28 p. (Evidence-based series; no. 3-17). [45 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Feb 21

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Genitourinary Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Genitourinary Disease Site Group (GU DSG) disclosed potential conflicts of interest relating to this systematic review and none were declared.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: guideline recommendations. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2008 Feb. 3 p. (Practice guideline; no. 3-17). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on July 16, 2008. The information was verified by the guideline developer on August 20, 2008.

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